Formamide

CAS #75-12-7
Swiss CD-1 mice, at 0.0, 100, 350, and 750 ppm in drinking water
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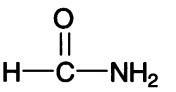

Formamide (F), an industrial solvent with likely human exposure, was tested for its effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol. It was nominated for testing based on isolated reports of antimitotic activity and developmental toxicity. Data on food and water consumptions, body weights, and clinical signs during a 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation phase at 0.0, 100, 350, and 750 ppm in drinking water. Based on mean body weight and average water consumption data, the estimated daily doses were approximately 19, 62, and 172 mg/kg for males and approximately 29, 98, and 218 mg/kg for females.

In the F_0 animals, both feed and water consumption increased for the high dose males (approximately 28 and 26% respectively). Two animals died or were killed moribund each in the low dose and middle dose groups. These deaths were attributed to injury by the mate or other nontreatment-related causes.

In the F_0 high dose animals during Task 2, mean litters per pair was reduced by 8%, while live pups per litter dropped by 28% compared to controls. Adjusted pup body weight and viability of these pups were both unaltered. The cumulative days to litter increased by 5 to 10 days in each of the first three litters in the high dose group, and stayed elevated for the last two litters as well. At the high dose, dam weights after each litter were reduced by approximately 7 to 8%; males at this dose were inconsistently reduced by 5 to 10%, compared to controls.

The last litter from all dose groups was nursed to weaning, and then mice were reared until a second-generation mating trial (Task 4) at 74 ± 10 days of age. Pre-weaning pup survival was not affected by F consumption by the dams. Pup weights were reduced by approximately 15% after weaning on postnatal day 21, though not significantly so beforehand. These differences were maintained throughout this Task. Feed and water consumption increased by 9 to 35% in the middle and high dose groups, with the high dose animals consuming more.

The data from Task 2 showed a clear reproductive effect, so a crossover study was performed. In this Task 3 mating trial, fewer high dose-treated females became pregnant (37 vs 90% for controls). However, no other end point measured in this trial was affected: the number of live pups per litter, pup viability, sex ratio, and the adjusted live pup weight were not affected. Pairs consisting of treated males mated to control females were not different from controls in any measure.

Twenty (controls) or 10 (treated) randomly-selected F_0 mice from each group were killed and necropsied after the F_1 pups were weaned and the Task 3 crossover completed. Body weights at necropsy were no different across groups. For males, there were no changes in the weights of major somatic organs or in reproductive organ weights. Epididymal sperm indices were unchanged. Similarly, there were no changes in weights of female liver, kidneys, or ovaries and no change in the length of the estrous cycle. Only 7 high dose F mice had "readable" cycles, compared to 20 controls. There were no significant microscopic findings in any tissue.

All dose groups were evaluated in the Task 4 mating trial. At the high dose, only two thirds as many females became pregnant as in the control group. In this group, the number of live F_2 pups per litter was reduced by 27% compared to controls. Adjusted live pup weight, viability, and sex ratio were all unchanged at any dose level.

After all pups were delivered and evaluated, the F_1 adults were killed and necropsied. Male terminal body weight was reduced by 14% at the high dose, the dose at which seminal vesicle weight dropped by 22%. There were no changes in epididymal sperm indices in any treated group. In high dose females, body weight was reduced by approximately 10%, while ovary weight was reduced by approximately 25% in both middle and high dose females. Also at the high dose, estrous cycle length was increased from a control value of 4.8 to 6.5 days. In this group, more than half the females had cycles that were longer than 11 days. There were no dose-related changes in microscopic lesions in any tissue evaluated.

In summary, these data show that formamide at 750 ppm in drinking water reduced murine fertility in both generations (fewer litters, smaller litters) and that the female was the affected sex (Task 3 crossover results and Tasks 2 and 4 estrous cycle data). These changes occurred in the presence of modest changes in body weight (both generations) and increases in food consumption.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB93109213**
Chemical: **Formamide**
CAS#: **75-12-7**
Mode of exposure: **Drinking water**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	100 ppm	350 ppm	750 ppm
General toxicity	Male, female	Male, female	Male, female
Body weight	— , —	— , —	—/↓ , —/↓
Kidney weight[a]	— , —	— , —	— , —
Liver weight[a]	— , —	— , —	— , —
Mortality	— , —	— , —	— , —
Feed consumption	— , —	— , —	↑ , —
Water consumption	— , —	— , —	↑ , —
Clinical signs	— , —	— , —	— , —
Reproductive toxicity			
x̄ litters/pair	—	—	↓
# live pups/litter; pup wt./litter	— , —	— , —	↓ , —
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight[a]	— , —	— , —	— , —
Sex accessory gland weight[a] (prostate, seminal vesicle)	— , —	— , —	— , —
Epidid. sperm parameters (#, motility, morphology)	— , — , —	— , — , —	— , — , —
Estrous cycle length	—	—	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	750 ppm	—

F_1 generation — Dose concentration →	100 ppm	350 ppm	750 ppm
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	— , —	— , —	— , —
Mortality	— , —	— , —	— , —
Adult body weight	— , —	— , —	↓ , ↓
Kidney weight[a]	— , —	— , —	— , —
Liver weight[a]	— , —	— , —	— , —
Feed consumption	— , —	↑ , —	↑ , ↑
Water consumption	↑ , —	— , —	↑ , ↑
Clinical signs	— , —	— , —	— , —
Reproductive toxicity			
Fertility index	—	—	—
# live pups/litter; pup wt./litter	— , —	— , —	↓ , —
Absolute testis, epididymis weight[a]	— , —	— , —	— , —
Sex accessory gland weight[a] (prostate, seminal vesicle)	— , —	— , —	— , ↓
Epidid. sperm parameters (#, motility, morphology)	— , — , —	— , — , —	— , — , —
Estrous cycle length	•	•	↑

Summary information	
Affected sex?	**Female**
Study confounders:	**None**
NOAEL reproductive toxicity:	**350 ppm**
NOAEL general toxicity:	**350 ppm**
F_1 more sensitive than F_0?	**No**
Postnatal toxicity:	**No**

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); — , —, no change in males or females. [a]Adjusted for body weight.